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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,404	06/21/2006	Jonathan S. Stamler	24862-516N01US	1777

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EXAMINER	
SAUCIER, SANDRA E	

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
04/06/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,404	STAMLER ET AL.	
	Examiner	Art Unit	
	Sandra Saucier	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *1,2,4-6,7 in part and 8 in part* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,7 in part, 8 in part, 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *7,8 in part* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/10,10/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending. Claims 3, 7, 8 in part, 9-12 are considered on the merits. Claims 1, 2, 4-6, 7 in part and 8 in part are withdrawn from consideration as being drawn to a non-elected invention.

Newly submitted claims 7 and 8 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims to treating a patient in need of nitric oxide therapy were withdrawn in the restriction requirement of 12/9/08.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 7, 8 in part are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

Claims 7 and 8 in part, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites "a disease of impairment of oxygen". This is not clear because the phrase "impairment of oxygen" is not art appreciated as a description of a genus of diseases. Furthermore, the phrase, "impairment of oxygen" does not make sense. Oxygen is a molecule, it is difficult to understand how one can damage this molecule and what diseases belong to such a genus. Thus, the metes and bounds of the claim cannot be determined.

Claim 8 recites said disease...is angina or stroke. Angina or stroke are not diseases, they are symptoms or signs of an underlying disease. Thus, the claim is indefinite because it does not further limit the claim upon which it depends.

Claim Rejections - 35 USC § 103

Claims 3, 7 in part, 9, 10, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30006 [N].

Claim 3 is directed to a method of treating a patient comprising co-infusing the blood substitute at a rate of 1-1000cc/hr and an inorganic nitrite at the rate of 0.01 to 10 micromoles per minute. The patient may be one losing blood.

WO 96/30006 discloses problems with the infusion of blood substitutes containing hemoglobin which causes vasoconstriction due to the scavenging of nitric oxide (page 1-2). Thus, the reference discloses methods to overcome this problem.

On page 5 a method for inhibiting the vasoconstrictive and nitric oxide depleting effects of hemoglobin and heme-containing based blood substitute composition by the concurrent systemic administration of nitric oxide or a compound which donates, releases or transfers nitric oxide. Such administration can be intravenously and **separately** with the blood substitute in one embodiment. An intravenous administration of a compound would reasonably be in an aqueous solution.

A compound which donates nitric oxide is sodium nitrite (page 10). On page 2, it is disclosed that cell-free blood substitutes are used for treating hemorrhage.

Therefore, the reference generically teaches the concurrent infusion of a hemoglobin-containing blood substitute and an NO donating compound, which may be sodium nitrite.

The reference lacks the disclosure of the specific concentration of nitrite to be administered.

Generally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation, *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range. *In re Hill*, 284 F.2d 955 (CCPA 1960). MPEP 716.02(d).

Claim 8 in part is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30006 [N] as applied to claims 3, 7, 9, 10, 12 above, and further in view of Remy *et al.* [U].

The claim is further directed to the treatment of a patient with a disease of impairment of oxygen.

Although the claim language makes no scientific sense, Remy *et al.* teach that clinical studies are under way in patients with hypovolemic shock, undergoing major surgeries and stroke.

Therefore treatment of patients with "a disease of oxygen impairment" with the method of WO 96/30006 would have been obvious when taken with Remy *et al.* who teach that patients with blood loss and stroke are being treated with red cell substitutes containing hemoglobin.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/30006 [N] as applied to claims 3, 7, 9, 10, 12 above, and further in view of US 4,820,269 [A].

With regard to claim 11, administration of compounds in saline or phosphate buffered saline is routine in the art of intravenous treatments. US 4,820,269 states in col. 1, l. 24, that intravenous solutions, such as saline or glucose solutions, are often use as carriers for the continuous administration of druges at controlled infusion rates.

Therefore, the administration of nitrite in a saline solution would have been obvious when the method of WO '06 was taken with US 4,820,269 who teach the use of saline as a drug carrier.

One of ordinary skill in the art would have been motivated at the time of invention to perform this method in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Response to Arguments

Applicant's arguments filed 1/22/10 have been fully considered but they are not persuasive.

Applicant argues that there is no objective reason provided by the cited reference that co-administration of a hemglobin blood substitute with an inorganic nitrite would be effective to decrease morbidity or mortality in patients needing a blood product transfusion. This argument has been considered, however, no objective evidence is present in the instant specification or application file demonstrating such a co-administration has an effect on morbidity or mortality. Thus, this argument is unpersuasive.

Applicants argue that WO '96 teach that a modified form of inorganic nitrite, acidified sodium nitrite, can be used to nitrosylate hemoglobin *in vitro*. However, applicants urge that inorganic nitrites are incapable of transfering NO unless the nitrite is be acidified. Applicants further urge that such acidfied nitrite would be toxic. In response, no such toxicity has been demonstrated

and further, Johnson *et al*. [V] teach IV infusion of acidifed sodium nitrite in a model of myocardial ischemia has a significant protective action during myocardial ischemia and reperfusion injury. No toxicity is described. Thus, applicants have failed to objectively support this particular argument. It is noted that the claim does not exclude the use of acidified inorganic nitrite and the primary reference does not stipulate that acidfied inorganic nitrite must be used in an intravenous method, only that the compound used donates, releases or transfers NO (page 5 of the reference) of which inorganic nitrite is one of this generic collection of compounds.

Applicants urge that the rate of infusion of inorganic nitrite is essential and critical since it is well recognized that hemoglobin is easily oxidized by inorganic nitrite resulting in methemoglobin which can be toxic. Applicants urge that the instant invention does not require the reaction of equimolar quantities of nitrite and hemoglobin. Please note that the claims do not require any quantity of hemoglobin because they do not stipulate the concentration of the hemoglobin in the solution to be used, merely a volume range. The argument appears to be directed to the relationship of the concentrations of the two infusates, but the claim limitations do not correspond to the argument because there is no concentration term for hemoglobin.

Applicants urge that the invention is: low concentrations of nitrite do not oxidize oxyhemoglobin, but rather combine with deoxygenated hemoglobin to store NO on the heme beta subunit of hemoglobin and to undergo several other reactions to form a hemoglobin product capable of NO delivery.

Firstly, this urging appears to be a reaction of inorganic nitrite which fulfills the functional language of " a compound which donates… or transfers nitric oxide" as recited on page 5 of the reference, which applicant above urged was not possible with inorganic nitrites which are not acidified. Secondly, this reaction as presented in the arguments has been demonstrated only *in vitro,* and no *in vivo* results have been provided which demonstrate applicants' urged unexpected results obtained from a separate infusion of inorganic nitrite and a

hemoglobin containing blood substitute. Therefore for the reasons above, the reference is still considered to render the invention obvious as claimed.

Objective evidence and a claim commensurate in scope with the presented evidence would advance prosecution.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
Primary Examiner
Art Unit 1651